

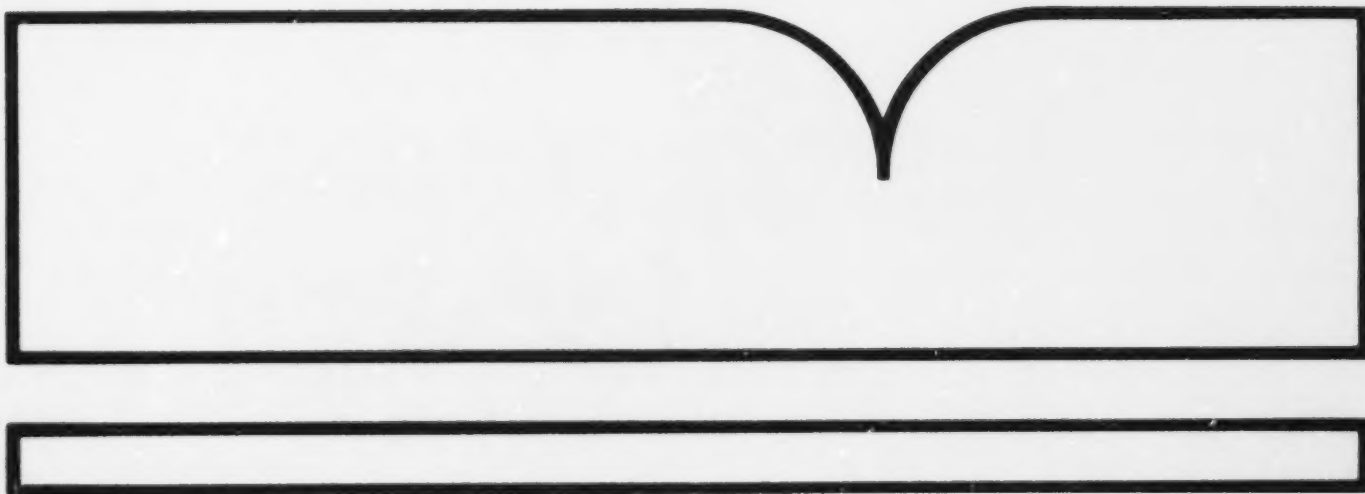
Multicompartment Kinetic Models for Lead
2. Linear Kinetics and Variable
Absorption in Humans without Excessive
Lead Exposures

Washington State Univ., Pullman

Prepared for

Health Effects Research Lab.
Research Triangle Park, NC

1985



U.S. Department of Commerce
National Technical Information Service

NTIS

TECHNICAL REPORT DATA <i>(Please read Instructions on the reverse before completing)</i>		
1. REPORT NO. EPA/600/J-85/425	2.	3. PB86-220381
4. TITLE AND SUBTITLE (Journal Version) MULTICOMPARTMENT KINETIC MODELS FOR LEAD II. Linear Kinetics and Variable Absorption in Humans without Excessive Lead Exposures		5. REPORT DATE 1985
7. AUTHOR(S) Allan H. Marcus		6. PERFORMING ORGANIZATION CODE
9. PERFORMING ORGANIZATION NAME AND ADDRESS Dept. of Pure and Applied Mathematics Washington State University Pullman, Washington		8. PERFORMING ORGANIZATION REPORT NO.
12. SPONSORING AGENCY NAME AND ADDRESS HEALTH EFFECTS RESEARCH LABORATORY OFFICE OF RESEARCH AND DEVELOPMENT U.S. ENVIRONMENTAL PROTECTION AGENCY RESEARCH TRIANGLE PARK, NC 27711		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/11
15. SUPPLEMENTARY NOTES John P. Creason BD/HERL/ Environmental Research (36) pp. 459-472 (1985)		
16. ABSTRACT Multicompartment models with constant fractional transfer rates have been fitted to experimental data on lead metabolism in four subjects studied by M. B. Rabinowitz, G. W. Wetherill, and J. D. Kopple (Science 182, 725-727, 1973; Environ. Health Perspect. 7, 145-153, 1974; Arch. Environ. Health 31, 220-223, 1976; J. Clin. Invest. 58, 260-270, 1976; J. Lab Clin. Med. 90, 238-248, 1977). Long-term retention is estimated for blood, soft tissue, cortical and trabecular bone pools, and for facial hair. The absorption of lead from diet is shown to change with time, but no evidence was found for other variable or nonlinear kinetic mechanisms of lead metabolism in humans without excessive lead exposure.		
17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
REPRODUCED BY NATIONAL TECHNICAL INFORMATION SERVICE U.S. DEPARTMENT OF COMMERCE SPRINGFIELD, VA. 22161		
18. DISTRIBUTION STATEMENT RELEASE TO PUBLIC	19. SECURITY CLASS (This Report) UNCLASSIFIED 20. SECURITY CLASS (This page) UNCLASSIFIED	21. NO. OF PAGES 16 22. PRICE

Multicompartment Kinetic Models for Lead

II. Linear Kinetics and Variable Absorption in Humans without Excessive Lead Exposures

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Received July 22, 1982

Multicompartment models with constant fractional transfer rates have been fitted to experimental data on lead metabolism in four subjects studied by M. B. Rabinowitz, G. W. Wetherill, and J. D. Kopple (*Science* 182, 725-727, 1973; *Environ. Health Perspect.* 7, 145-153, 1974; *Arch. Environ. Health* 31, 220-223, 1976; *J. Clin. Invest.* 58, 260-270, 1976; *J. Lab. Clin. Med.* 90, 238-248, 1977). Long-term retention is estimated for blood, soft tissue, cortical and trabecular bone pools, and for facial hair. The absorption of lead from diet is shown to change with time, but no evidence was found for other variable or nonlinear kinetic mechanisms of lead metabolism in humans without excessive lead exposure. © 1985 Academic Press, Inc.

1. INTRODUCTION

Environmental health standards for lead have generally used the concentration of lead in blood as the criterion for potentially adverse health effects. The blood lead criterion is likely to remain in use in the United States, at least in the near future. Yet there is a growing awareness that blood lead only measures recent exposures. Many of the effects of lead are expressed in peripheral tissues, e.g., heme synthesis (bone marrow, liver), excretion (renal tubules), and neurotoxic responses (brain). The kinetics of lead distribution among tissues must then be considered.

Unfortunately, lead concentrations in peripheral tissues (i.e. soft tissues and organs other than blood) cannot be routinely monitored. Thus, they cannot be routinely controlled to safe levels. We must therefore depend on predictive models (usually in mathematical or algorithmic form) to relate what can be monitored and controlled with those effects that cannot be measured directly.

Any mathematical model is a caricature of reality. One can only hope that enough details have been included to render the portrait recognizable. We will here present some analyses of published data sets in which the initial exposures to lead have been measured and controlled. The biological concentrations have been measured at a sufficiently large number of time points for several organs to allow reasonable estimates of the parameters that characterize the movement of lead from one pool to another. As is usual in compartmental analysis, the pools cannot be unambiguously identified with specific organs or organ systems in general unless biological concentrations are available to confirm the model predictions. We have chosen data sets in which at least some such identifications

seem plausible. We have also used only data sets for individual subjects, since the parameters for lead distribution may vary substantially from one subject to another.

2. DATA ANALYSIS METHODS

We analyzed data for subjects A, B, D, and E in the series of long-term studies carried out by M. Rabinowitz *et al.* at UCLA (1973; 1974; 1976a, b; 1977); these authors also provided useful additional clarification and information about these significant experiments. The data sets included total blood lead, blood lead labeled with ^{204}Pb and ^{207}Pb tracers, total and labeled lead concentrations in hair, and in the trabecular and cortical bones of the iliac crest. The exposure sources included dietary lead, air lead, and cigarettes. Since we are interested in long-term kinetics, we did not use data for subject C which were reported for only 10 days.

These data are of particular relevance in determining the approximate linearity of the kinetic model, since the tracer exposures were turned on and off at various times, the air lead exposures were turned off and on for subjects B, D, and E when they were sequestered in a "clean" room for 40, 25, and 50 days, respectively, and the controlled diet in a metabolic ward was changed to *ad lib.* diets for subjects A, B, and D when they left the ward. These time-varying patterns of exposure allow consideration of responses at different dose levels, usually the most effective method for testing linearity. The experiments extended over a sufficiently long period to allow preliminary estimation of the kinetics and volumes of the cortical and trabecular bone pools. These studies suggested that some of the absorption parameters may have changed over time.

The tracer data provided good information about low-level kinetics because there were negligible preexisting tissue concentrations of these stable isotopes. Kinetic analysis of whole blood lead concentrations can become difficult when the subject's tissue lead distribution is not in equilibrium. Because lead is retained in skeletal tissues for a long time, whole blood lead in human subjects may *never* achieve a genuine equilibrium level. We have seen evidence of this in a kinetic analysis of the experiments in (Griffin *et al.*, 1975). Thus, tracer data is desirable in studying lead kinetics. However, any plausible nonlinear kinetic mechanisms would likely be responding to the total lead content of the blood rather than to the small quantity of added tracer, so whole blood lead levels were also required to explore some hypotheses about nonlinear kinetics.

Rabinowitz *et al.* (1973, 1976a, b) fitted three-pool models to their ^{204}Pb tracer data. The pools were tentatively identified as (mainly) blood, soft tissue, and bone. The "blood" pool had a larger mass than could be attributed to the blood alone and thus most likely included the more labile soft tissues. Similarly, the soft tissue pool may have included some of the more rapidly exchanging bone tissues.

We believed a more detailed model could be fitted to the same data. By using all of these data, including ^{207}Pb tracer and total lead in blood, the estimated

parameters of the model should be more reliable if the model is correct. We also thought that use of the bone lead and hair lead data would lead to improved estimates of kinetic parameters in bone and hair since blood lead fluctuations would be taken fully into account. Such models do not require any ad hoc assumptions about bone resorption rates and blood-bone recirculation.

The three-compartment model in (Rabinowitz *et al.*, 1976) was in effect only a two-compartment model since the bone lead contribution to blood was assumed nearly constant due to the large lead content and long residence time of lead in bone. This two-compartment model was fitted only to the ^{204}Pb tracer data. We knew in advance that our model would not fit the ^{204}Pb data quite as well as this model because our model forced a common set of kinetic parameters for both ^{204}Pb and ^{207}Pb tracers, as well as for total blood lead. If the assumption of common kinetic parameters was wrong, then some component of the fitted models would be in serious disagreement with the data.

It also appeared useful to estimate the air lead intake without prior assumptions about lung deposition and breathing rate (Rabinowitz *et al.*, 1977; Chamberlain *et al.*, 1978). The varying pattern of diet and air exposures and estimation of endogenous lead pools in skeleton and tissues permitted independent estimation of air lead absorption with other sources accounted for.

As a preliminary step in analyzing these data we assumed that the quantity of lead in each of the pools was governed by a coupled system of first-order differential equations with constant coefficients. The basic rate parameters are the fractional exchange coefficients $k(i,j)$ representing the fraction of lead in compartment j that is transported to compartment i , per day. Several sets of assumptions about the non-zero rate coefficients were tested. Several sets of assumptions about the masses $M(i)$ of the pools were also tested. See Appendices 1 and 2 for the equations.

The theory of linear compartmental systems is well known (e.g., Jacquez, 1972). Such models readily lend themselves to empirical data analysis by use of computer programs for nonlinear least-squares estimation (Berman and Weiss, 1962). We used the SAAM 27 program (Berman and Weiss, 1978) with fractional standard deviation weighting. This program provided particularly convenient control language for modeling changes in dosage parameters over time. The same program also fitted the nonlinear models.

Because of the large number of parameters to be estimated, it was not always possible to obtain reliable estimates of all parameters at a single pass. Parameters were usually estimated in stages, with most pool sizes (especially the blood pool) held fixed at the last analysis. The initial uncertainty (initial estimate of standard error) of each parameter was taken as 100% of the initial estimate of the parameter value. In almost all cases the final estimates had appreciably smaller standard errors than the initial estimates. We believe these apparently subjective features of the analysis fairly reflect prior knowledge about plausible values of parameter estimates based on earlier studies (Rabinowitz *et al.*, 1973; 1974; 1976a, b; 1977; Batschelet *et al.*, 1979; Marcus, 1979).

3. RESULTS

Several compartmental structures were tested. It is well known that more than one structural model or set of parameters may be found to fit a complex compartmental model in which most of the peripheral compartments are not observed, as is the case for the Rabinowitz data. Thus we cannot claim that the models proposed here are unique, much less "correct." We do claim that the models are physiologically plausible and fit these data better than the other plausible models we have tried.

A parsimonious nine-compartment model for the Rabinowitz data is shown in Fig. 1. Its parameters are shown in Tables 1-5. The pool in Fig. 1 identified as "Soft Tissue" probably consists of several pools with similar turnover rates that

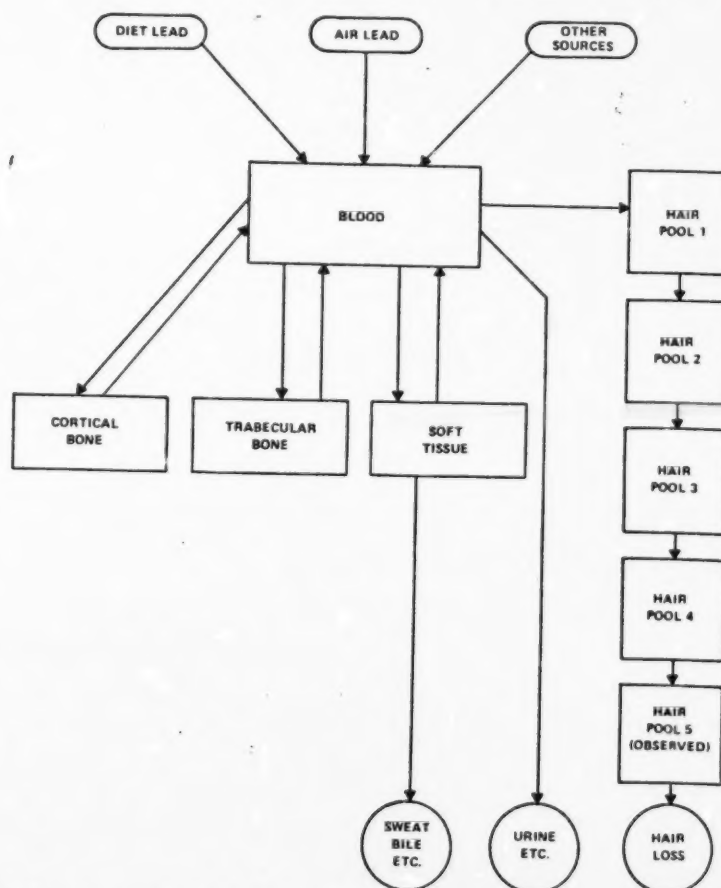


FIG. 1. Compartmental model for lead in man, based on analysis of data presented by Rabinowitz *et al.* (1973; 1974; 1976a, b; 1977).

TABLE I
ESTIMATED RATE PARAMETERS

Pool (from/to)	Subject							
	A		B		D		E	
Blood/tissue	1.98	(88)	2.17	(58)	1.96	(71)	1.23	(62)
Blood/hair	2.36	(62)	3.61	(72)	0.256	(65)	—	
Blood/cortical bone	3.17	(35)	7.32	(55)	8.66	(61)	3.97	(61)
Blood/trabecular bone	0.661	(41)	2.09	(54)	5.73	(55)	1.13	(63)
Blood/urine	31.83	(8.2)	16.30	(30)	6.19	(75)	29.80	(9.2)
Tissue/blood	0.439	(91)	7.54	(66)	0.466	(98)	0.953	(74)
Tissue/bile, etc.	2.72	(89)	4.70	(88)	2.52	(102)	1.74	(62)
Hair/next hair	56.5	(4.6)	79.4	(6.6)	124.4	(2.4)	—	
Final/hair loss	455.8	(59)	563.9	(63)	232.6	(94)	—	
Cort. bone/blood	0.0206	(100)	0.0609	(95)	0.0268	(86)	0.0216	(100)
Trab. bone/blood	5.17	(33)	0.945	(73)	1.38	(42)	1.66	(56)

Note. Values are given as estimated rate parameters (10^{-3} days $^{-1}$); percent standard errors are given in parentheses.

cannot be separated without specific organ concentration data. However, the present analysis did not make use of the reported data on other sources of elimination (sweat, saliva, sputum, gastric secretion, bile, pancreatic secretion, nails) that might help to localize these subpools (Rabinowitz *et al.*, 1976a, b).

The complicated catenary submodel for facial hair is needed to account for the observed delay in the appearance of tracer lead in facial hair. It is assumed that each of the five subpools is of the same size and has the same transfer rate to the next pool. This model was adequate for subjects A and B, but less adequate for facial hair lead in subject D. It is not known if this submodel can be used for scalp hair as well.

Bone lead was adequately explained for subjects A and B, but each subject had only two data points each (tracer and total lead) from cortical bone and two from trabecular bone.

All tracer and total blood lead concentrations were well fitted by the model. Observed and predicted ^{204}Pb concentrations in blood are shown in Figs. 2-5. ^{207}Pb and total blood levels are equally satisfactory.

TABLE 2
ESTIMATED POOL SIZE

Pool	Subject							
	A		B		D		E	
Blood	5954	(33)	9486	(2.9)	9080	(82)	5595	(27)
Hair (each of 5)	1.89	(84)	2.88	(88)	1.47	(67)	—	
Cortical bone	2236	(10)	4587	(56)	—		—	
Trabecular bone	241	(51)	1357	(56)	—		—	

Note. Estimated pool size is given in grams; percent standard errors are given in parentheses.

TABLE 3
ESTIMATED INITIAL LEAD BURDEN BY POOL

Pool	Subject							
	A		B		D		E	
Blood	1514	(33)	1681	(7.1)	1666	(5.9)	960	(27)
Soft tissue	2356	(100)	2155	(75)	1455	(98)	2738	(61)
Hair (first 4) ^a	317	(62)	128	(68)	—	—	—	—
Cortical bone	33200	(95)	39958	(56)	40000	(100)	33000	(100)
Trabecular bone	3318	(44)	5771	(53)	10787	(47)	9422	(138)

Note. Estimated initial lead burden is given in micrograms; percent standard errors are given in parentheses.

^a Calculated by quasiequilibrium assumption.

In order to achieve a satisfactory description of blood lead changes, it was necessary to assume that the rate of absorption of diet lead increased by 1 or 2% after 30 to 60 days, and increased substantially again after 120 to 160 days. This could also have been achieved by changing the fractional transfer rates, but the present approach involves far fewer changes of parameters with time. Examination of Table 4 shows the similarity of increased absorption among all four subjects. The actual time of changed diet absorption was selected by the author from visual examination of data plots such as Figs. 2-5.

A formal significance test of the hypothesis that gut absorption changed at the indicated times was based on the following technique. Suppose that the weighted residual sum of squares or "error" sum of squares for a model with p adjustable parameters is denoted $SSE(p)$. Suppose this model is included in a more comprehensive model with q additional adjustable parameters; e.g., with three absorption coefficients rather than one, $q = 2$. Denote the residual sum of squares of the larger model by $SSE(p + q)$. This should be smaller than $SSE(p)$ since we can always do at least as well by fitting the larger model. Then the statistic

$$F = ((SSE(p) - SSE(p + q))/q) / (SSE(p + q)/(n - p - q))$$

TABLE 4
DIETARY ABSORPTION OF LEAD (NONFASTING)

	Subject							
	A		B		D		E	
Interval (days)	0-61		0-53		0-33		0-42	
Fraction absorbed	0.0673	(32)	0.0566	(3.4)	0.1004	(3.7)	0.0392	(27)
Interval (days)	61-161		53-149		33-119		42-106	
Fraction absorbed	0.0878	(32)	0.0771	(4.2)	0.1122	(4.0)	0.0444	(27)
Interval (days)	161-407		149-209		119-275		—	
Fraction absorbed	0.1348	(34)	0.1379	(22)	0.1943	(16)	—	

Note. Values indicate dietary absorption of lead during the intervals indicated; percent standard errors are given in parentheses.

TABLE 5
ESTIMATED LEAD INPUT

Source	Subject							
	A		B		D		E	
Ward and ambient air	19.40	(42)	13.49	(40)	6.66	(88)	6.35	(36)
Clean room and ambient air	—		2.29	(88)	1.37	(86)	1.00	(60)
Ad lib diet	360	(100)	305	(23)	209	(19)	—	

Note. Lead input is given in micrograms/day; percent standard errors are given in parentheses.

can be used to test the hypothesis that the larger model is no better than the smaller model by rejecting the hypothesis if F is larger than the appropriate percentile of Fisher's F distribution with q numerator and $n - p - q$ denominator degrees of freedom (Gallant, 1975). Here, n is the number of observations, with the sum of the weights adjusted to n .

As seen in Table 6, the change of gut absorption was statistically significant at the 5% level for subjects A, B, and E, and large but only significant at the 10% level for subject D. These tests are essentially independent of each other, hence

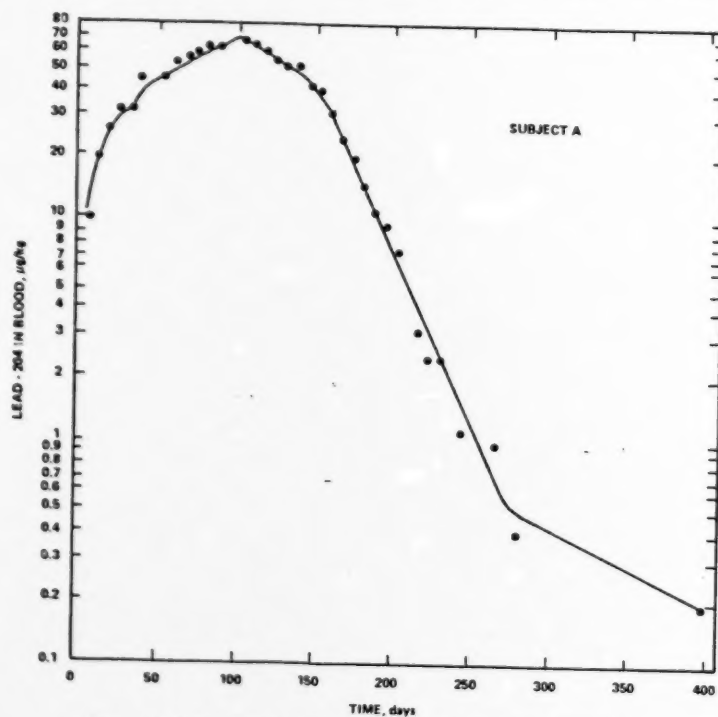
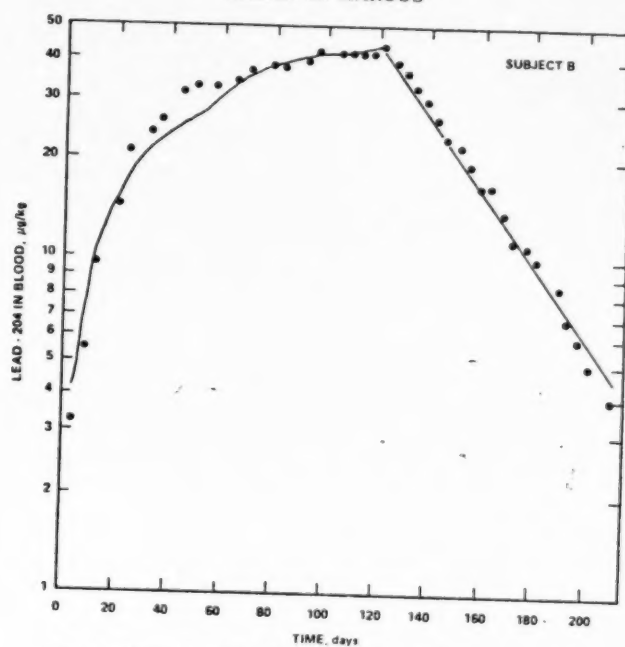
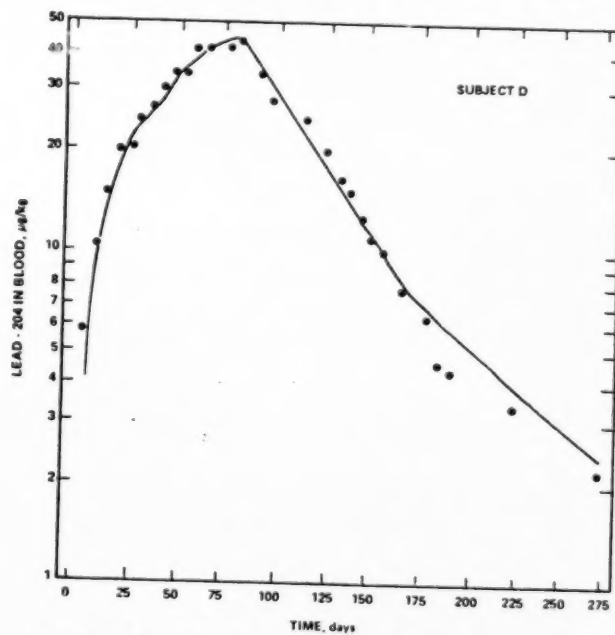


FIG. 2. Observed and predicted blood lead (^{204}Pb) in subject A.

FIG. 3. Observed and predicted blood lead (^{204}Pb) in subject B.FIG. 4. Observed and predicted blood lead (^{204}Pb) in subject D.

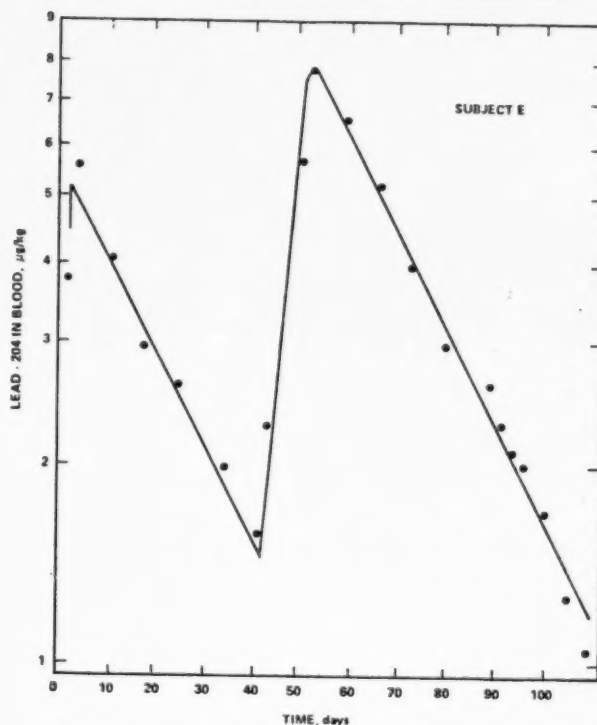


FIG. 5. Observed and predicted blood lead (^{204}Pb) in subject E.

the conclusion is even more compelling. On the other hand, the subjective choice of the times of the changes may have inflated the apparent significance of the result, but it was not feasible to also include these change times as adjustable parameters. None of the parameters of lead distribution changed significantly.

This statistical test was also used with the nonlinear models described in Appendix 2. All nonlinear models include the linear kinetic model as a special case

TABLE 6
TEST OF HYPOTHESIS THAT GUT ABSORPTION DOES NOT CHANGE WITH TIME

Subject	Observations <i>n</i>	Parameters		$\text{SSE}(\rho) \times 10^6$	$\text{SSE}(\rho + q) \times 10^6$	<i>F</i>
		<i>p</i>	<i>q</i>			
A	97	19	2	9.198	8.080	5.26*
B	106	21	2	342.59	287.73	7.91*
D	77	18	2	246.21	227.15	2.39**
E	42	13	1	1.240	0.904	10.81*

* Rejected at the 5 percent level of significance.

** Rejected at the 10 percent level of significance.

with $P(10) = 0$. None of the nonlinear models provided a significantly better fit to the data.

4. DISCUSSION

Compartmental models with nine pools provided adequate descriptions of some of the available data for kinetics of lead in man. As with any multicompartmental model in which there are compartments that are only indirectly measured by their effects on other observable compartments, the identification of the pool with any specific organ system is highly tentative. Nonetheless, estimation of pool content and transfer rates may be helpful in physiological identification. The derived model structure is of course not unique, particularly in view of the near mammillary structure of the hypothesized models (Travis and Haddock, 1981), and there are other models which could reproduce the same pattern of concentrations. No amount of curve fitting and modelling can provide the information derived from biopsy data in peripheral tissues. But until such data become available, the present models may provide a framework for predicting lead distribution in humans.

The human subjects were exposed to air lead and diet lead inputs whose blood lead changes varied by an order of magnitude. There was no evidence suggesting that changes in blood lead were not proportional to dose absorbed from the external environment; thus, we may assume that lead kinetics are approximately linear over this interval. The general adequacy of the fitted models suggests that the kinetic models are approximately first order as well, over this dose interval.

A considerable amount of attention has been given to the possibility of nonlinear mechanisms that may be reflected in the empirical curve fitting of whole-body lead retention functions $R(t)$ to power laws and other nonexponential functions (Hursch, 1973; Marcus, 1979; Matsubara *et al.*, 1981). In the first paper in this sequence we have demonstrated that a linear model based on diffusion of lead through bone may be adequate to explain the apparent power-law lead retention function observed in beagle dogs (Marcus, 1983; 1985). However, bone diffusion models were not fitted here because the total duration of these blood tracer measurements (106 to 407 days) was a much smaller fraction of the organism's lifetime than was the duration of the beagle dog studies (1100 to 1497 days). In any case, bone diffusion kinetics can be adequately approximated by a linear kinetic model with several bone components. In particular, bone kinetic parameters for subjects A and B could be estimated from a few observations. The inference of similar parameter values for subjects D and E is purely by analogy.

A number of nonlinear mechanisms in soft tissue lead metabolism are known to exist. Gut absorption of lead in rats is known to have both saturable and nonsaturable pathways (Aungst *et al.*, 1981). This is not apparent in Rabinowitz's data (Rabinowitz *et al.*, 1980). The increase in gut absorption over time may suggest two or more methods of lead handling in the gut. This could explain the change in tracer absorption, but not the similar pattern for total lead absorption. It seems more likely that the carefully controlled content of the metabolic ward diet for these subjects altered their usual levels of both vitamins and essential

elements such as calcium, iron, zinc, and phosphorus, and thus modified their usual gut absorption or bone resorption parameters over time.

High levels of blood lead are known to disturb many functions such as heme synthesis and renal clearance. It seems likely that many kinetic parameters are different at high levels of blood lead, but that under reasonably constant conditions the kinetic parameters of normal lead metabolism are nearly constant. Chamberlain and Heard (1981) and Chamberlain (1983) discuss evidence for increased renal clearance at high blood lead levels. Our analysis suggests that if either renal clearance or absorption into a relatively immobile pool such as bone is increased at high blood lead levels, significant changes occur only at blood levels much above 30 $\mu\text{g}/\text{dl}$.

Raghaven *et al.* (1980) discuss the presence of lead-binding proteins in lead toxicity. The role of inducible lead-binding proteins in normal lead metabolism is not known.

The partition of lead between blood plasma and red blood cells is of interest in determining acceptable levels of blood lead. McRoberts (1973) demonstrates the importance of blood lead fractionation in establishing criteria for inorganic lead poisoning. It is likely that non-first-order kinetic models apply to erythrocyte binding of lead, either by site-limited or rate-limited mechanisms. In the next paper of this sequence (Marcus, 1985b) we examine the data presented by DeSilva (1981) that clearly show the importance of nonlinear kinetic mechanisms in the partition of lead between plasma and erythrocytes.

A more fundamental biochemical description of the deep erythrocyte pool might be helpful. Clarkson and Kench (1958) have suggested that certain second-order kinetic processes may play a role in the interaction of lead with erythrocytes. The time scale of such processes may be sufficiently short relative to the duration of the experiments analyzed here that there is little error in assuming first-order kinetics for purposes of environmental impact assessment.

We have not distinguished diffusible plasma lead from plasma protein-bound lead (Baloh, 1974). The binding mechanisms may again be nonlinear. When binding mechanisms are saturated, a large increase in the tissue burden of lead may accompany a proportionate increase in diffusible plasma lead only, with a correspondingly smaller change in both erythrocyte lead and total blood lead.

We have also ignored the role of extracellular fluid. As noted elsewhere (Stover, 1959; Chamberlain *et al.*, 1978), soluble inorganic lead is rapidly shared between plasma and extracellular fluid, and is more slowly attached to red blood cells (RBC). However, this withdrawal into RBC then draws some of the lead back into the plasma, producing an apparent "rebound" of plasma concentration after some minutes. It is not clear that such an effect is important in modelling lead absorption from the environment, since both the lungs and the gut have time scales for absorption of several hours (Chamberlain *et al.*, 1978) that tend to "filter out" high-frequency variations in air lead and ingested lead.

Finally, we can only agree with Rabinowitz *et al.* (1967a) that lead handling in rodents appears different from that in humans. This is also suggested by our beagle analyses (Marcus, 1983; 1985a), but differences in the data collected do

not permit more precise quantification of this difference. Comparable multispecies experiments are still needed, especially those involving lead exposures high enough to induce potentially adverse effects.

ACKNOWLEDGMENTS

I am most grateful to Dr. Michael Rabinowitz for his many helpful comments and to the referees for their many constructive comments. This work was completed at the Health Effects Research Laboratory of the U.S. Environmental Protection Agency where the author was a National Research Council Resident Research Associate. I am grateful to Mrs. Barbara Crabtree for retyping the manuscript.

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APPENDIX 1

Mathematical Model for Rabinowitz Study

Let

- $X(1)$ = mass of lead in blood
 $X(2)$ = mass of lead in soft tissues
 $X(3)$ = mass of lead in cortical bone
 $X(4)$ = mass of lead in trabecular bone
 $X(5)$ = mass of lead in first facial hair subpool
 $X(6)$ = mass of lead in second facial hair subpool
 $X(7)$ = mass of lead in third facial hair subpool
 $X(8)$ = mass of lead in fourth facial hair subpool
 $X(9)$ = mass of lead in fifth facial hair subpool.

Then

- (A1) $dX(1)/dt = k(1,2)X(2) + k(1,3)X(3) + k(1,4)X(4) - (k(2,1) + k(3,1) + k(4,1) + k(5,1) + k(0,1))X(1)$
 + absorbed lead,
- (A2) $dX(2)/dt = k(2,1)X(1) - (k(1,2) + k(0,2))X(2)$
- (A3) $dX(3)/dt = k(3,1)X(1) - k(1,3)X(3)$
- (A4) $dX(4)/dt = k(4,1)X(1) - k(1,4)X(4)$
- (A5) $dX(5)/dt = k(5,1)X(1) - k(6,5)X(5)$
- (A6) $dX(6)/dt = k(6,5)X(5) - k(6,5)X(6)$
- (A7) $dX(7)/dt = k(6,5)X(6) - k(6,5)X(7)$
- (A8) $dX(8)/dt = k(6,5)X(7) - k(6,5)X(8)$
- (A9) $dX(9)/dt = k(6,5)X(8) - k(0,9)X(9).$

APPENDIX 2

Mathematical Models for Nonlinear Mechanisms

Let $X(1)$ - $X(9)$ be defined as in Appendix 1.Let $1/P(10)$ be the mass of lead in a pool with nonlinear kinetics at which some

rate coefficient changes by 100% from its low-concentration value ($P(10) = 0$ is linear kinetics).

Model for Rate-Limited Gut Absorption

Replace "absorbed lead" in (A1) by $(\text{absorbed lead}) = (\text{ingested lead}) / (1 + P(10) \times (\text{ingested lead}))$.

Model for Increased Plasma Clearance

Replace $k(0,1)$ in (A1) by $k(0,1) \times (1 + P(10) \times X(1))$.

Model for Increased Absorption

Replace $k(2,1)$ in (A1-2) by $k(2,1) \times (1 + P(10) \times X(1))$.

Model for Rate-Limited Blood Uptake

In (A1-4) replace $k(1,j)$ by $k(1,j) / (1 + P(1,j) \times X(j))$ for $j = 2,3,4$, and "absorbed lead" by $(\text{absorbed lead}) / (1 + P(10) \times \text{absorbed lead})$.

Model for Site-Limited Blood Uptake

In (A1-4) replace $k(1,j)$ by $k(1,j) \times (1 - P(1,j) \times X(j))$ for $j = 2,3,4$, and "absorbed lead" by $(\text{absorbed lead}) \times (1 - P(10) \times \text{absorbed lead})$.

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